THE BOOK WAS DRENCHED

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PROBLEMS IN FILARIASIS

BY

T. BHASKARA MENON, M.D. (Madr.), M.R.C.P. (Lond.),
*Pathologist to the Government Royapuram Hospital, Madras,
Lecturer in Pathology, Stanley Medical School.*

WITH A FOREWORD BY

MAJOR-GENERAL SIR FRANK POWELL CONNOR, *Kt.,*
D.S.O., K.H.S., F.R.C.S., I.M.S.,
Surgeon-General with the Government of Madras.

FOREWORD.

Filariasis still remains in South India and in many other parts of the world, as a vast unsolved problem causing misery and disability to millions of human beings.   This does not mean that we know little or nothing about this affection, for we know a great deal; but, much more has yet to be discovered before the problem can be said to be mastered. Dr. Bhaskara Menon, in the Maharajah of Travancore's Curzon Lectures (University of Madras), 1934-35, gives us an up to date account of this disease and discusses his own views and his own work.   Light is beginning to be shed on dark places and we can reasonably hope that before long the whole field will be illuminated.

Dr. Bhaskara Menon in his three lectures divides up the subject as follows:—

Lecture I—History, epidemiology, clinical types, symptomless filariasis, gaps in the life cycle.

Lecture II—Microfilarial periodicity, pathological problems of filariasis.

Lecture III—Pathology of elephantiasis, methods of diagnosis, problem of treatment, need for future work.

Under each of these headings Dr. Bhaskara Menon gives an account of the recent work, and in many cases his own valuable work, on the subject. I have for many years studied the complicated problem of

filarial infection in human beings, prevention and treatment, and have therefore followed these discussions on each aspect of the subject with great interest. I am sure others will do the same. I have always thought of Filariasis as a much neglected subject, considering the fascinating field of study which it provides to research workers in the tropics, and I hope Dr. Bhaskara Menon will pursue his investigations and induce others to follow his example.

MADRAS,
August 1935. }   F. P. CONNOR.

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PROBLEMS IN FILARIASIS

In trying to explain the gaps in our knowledge of filariasis, one is at the outset faced with the intricacies of a disease complex, that has repeatedly puzzled the pioneer workers in tropical medicine. Nevertheless, the subject is one of extreme importance, particularly to us here in South India, with many endemic foci in the coast and along the river banks. It is also prevalent in large towns and suburban areas; and, because of the difficulties in treatment and prophylaxis, is a real menace to public health. Filariasis is a danger, not because of any immediate fatal results, but of the ultimate consequences of infection, resulting often in invalidism and incapacitating effects on the working man.

I have chosen the subject, not because we are yet in a position to solve all the difficulties in understanding the disease, but to bring before you an instance of a tropical disorder where much work has to be carried out. There has been an idea and it has also been expressed that most of the problems in tropical medicine have already been solved and the work that remains is only for co-ordination and a study of detail. While it is no doubt true, that much has been done, much more remains to be accomplished. Osler's remark 'the little done the great undone', remains true even to-day.

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If one were to study the problems of a disease, where so little is known, a short *résumé* of known facts may not be out of place.

It is a curious anomaly that, though the first descriptions of elephantiasis are found in ancient Hindu text, the term *Elephantiasis arabum* is used to designate the disease. It was recognised as a separate entity in the Vedic and Brahminic periods. Sushruta,[1] in the 6th century B.C., described the disease under the term "Shli padam", meaning "stone like leg". He described the involvement of the thighs, the knee joints, the legs and the inguinal regions. Three types of the disease are mentioned; one, with spasmodic attacks of pain in the affected part, followed by rupture of the skin; another, with attacks of fever; a third, where the affected tissues become white and glossy, while large nodules and papillae make their appearance. Vāgbhāta[2] in the 2nd century A.D. described how the disease makes its appearance in the inguinal region with 'kapha dosha' (humoral disturbance) and how it spreads through the flesh and blood and settling in the foot slowly causes a hard swelling. Mādhavakara,[3] the Hindu pathologist of the 7th century writes:—

य. सज्वरो वङ्क्षणजोभृशार्थिः शोथो नृणां पादगतः क्रमेण ।
तच्छलीपदं स्यात्करकर्णनेत्रशिश्नाघ्रनासास्वपि केचिदाहुः ॥

"One with fever and a very painful swelling starting in the inguinal region and gradually coming down to the feet, that is 'Shlipadam'. Some say that the swelling may also affect the hands, the ears, the eyes and the genitalia".

In Europe, the disease was confused by Galen with leprosy for Celsus had applied the name 'elephantiasis' to this condition. The disease was fully described by the Arabian physicians Rhazès and Avicenna. In India, however, in the priest ridden obscurantism following the Mohammedan invasion, all attempts at direct observation and experimental work died down among the Hindu physicians and we find little progress in the study of the condition up to the European period. Elephantiasis in Cochin and the Malabar coast was first described by Clark[4] in 1709, under the term ' Cochin leg'. This no doubt gave rise to the name 'Phlegmasia malabarica'. Tropical elephantiasis was differentiated from Elephantiasis græcorum by Hillary[5] in 1750, but the true nature of the condition was not suspected until the parasites were discovered. The microfilariae were first discovered by Wucherer[6] (1866), in the urine, and the parent worms by Bancroft[7] (1876) ; thus the name *Wucheraria bancrofti* is used to-day. The presence of microfilaria in the blood was demonstrated by Lewis[8] (1872). To Manson[9] (1878), belongs the credit of the discovery of the intermediate host, the mosquito. He traced the metamorphosis of the parasite[10] (1883) in the mosquito's stomach and also tracked the parent worms to their fastness in the lymphatic vessels[11] (1880). Manson put forward the hypothesis that, after development in the mosquito, the infective larvae escaped into drinking water, during oviposition or after death. The infective forms were demonstrated in the proboscis by Low[12] (1900). Fülleborn's experiments on *Filaria immitis*

conclusively proved, at least in the dog, that the infective larvae left the proboscis and were deposited in the skin during biting. The phenomenon of filarial or microfilarial periodicity was brought to light by Manson,[13] who explained that this was an adaptation to the feeding habits of the mosquito (1899), the microfilariae retiring to the heart, the great vessels and the lungs during the day. The association between filarial disease and elephantiasis, long disputed and often denied, was first suggested by Manson and subsequent work has completely proved his case. Other notable contributions to the study of the disease are the descriptions of the parent worms by Cobbold,[14] and of the microfilaria by Lewis, the researches of Low and also of Fülleborn regarding the mode of attack of the infective larvae, the researches of Bahr[15] in Fiji, of Cruickshank and Wright[16] in Cochin and the recent work of O'Connor and his colleague in Porto Rico—to mention only a few.

AN ENDEMIOLOGICAL PROBLEM

While the tropical and subtropical distribution of filariasis and its prevalence along the coast lying districts and river banks is capable of explanation, a puzzling feature has been the peculiar endemicity of the disease in those countries where it is prevalent. Small circumscribed foci are met with, where the infection rate is very high, but neighbouring areas with very similar climatic conditions show only a lower incidence. Daniels[17] (1908) noticed this unequal distribution in the southern end of Lake Nyassa as compared with the

northern end, while Low's studies[18] (1911) in the West Indies showed that some islands were very heavily infected, while neighbouring islands escaped. Bahr[19] noticed a similar erratic distribution in Ceylon. In the Malabar coast there are certain well defined foci in British Cochin and Travancore while neighbouring areas in the interior do not show such a high incidence. Here, in Madras, Saidapet which is almost a suburb is an endemic focus, while in Madras city filariasis has only a sparse distribution. Korke[20] (1930) points out that the distribution in India is highest in the sea coast belt, high in the Gangetic plain and lowest in submountable areas. He compares the heavy infection in Bihar and Orissa with the comparative rarity of filariasis in Punjab and argues that a low altitude and associated rice cultivation favour the occurrence of endemic filariasis. Korke[21] (1930) holds that the physiography is the important feature in this connection. Filariasis in India would be predominant in areas like the Coromandel coast, Northern Circars, Konkan and the Malabar coast and less in the Gangetic and Indus plains which are physiographically on a higher level than the coastal belt. He admits, however, that, in certain places, these factors cannot explain the incidence. The capricious distribution of filariasis has been noticed in Samoan islands, in Porto Rico and in the affected districts in China. If it were a question of the intermediary host, *Culex fatigans,* first incriminated by Manson, is almost ubiquitous. Various species of mosquitoes, *Aedes variegatus var pseudo-scutellaris* in Fiji, some species of *Mansonia* and also of *Anopheles*

are all capable of transmitting the disease and have been found infected in nature. Recently, Hu and Chang[22] have incriminated *Culex pipiens var pallens,* in Woosung district in China.

The explanation that has been offered is that high atmospheric temperature and humidity are essential for the complete development of the larval form in the mosquito. In other cases, as noted by Ashburn and Craig (1906)[23], thoracic development may stop short and infective forms may not pass forward into the proboscis. Fülleborn's[24] experiments show that the infective larvae require, after leaving the proboscis of the mosquito, a humidity and moisture for penetration; in a dry atmosphere, they are destroyed. Sunder Rao and Iyengar[25] (1930) have brought forward evidence to show that high atmospheric temperature and humidity gave a high infection rate in *Culex fatigans*. Can this be the whole explanation? It is difficult to decide why filariasis is so rife in British Cochin while it is much less prevalent in Ernakulam foreshore, where almost identical atmospheric and geographical conditions prevail. Paddy cultivation can hardly have any special influence in the small town of Cochin, since it is universal in the Malabar coast. As another instance, I may say that the peculiar distribution is very marked in a small village in Cochin State, Idapalli, where filariasis seems to stop short on the banks of a fresh water stream. There seems to be no doubt that atmospheric temperature has a good deal of influence on the rate of development of the larvae in the mosquito. Thus Bahr[26] found that the full development takes

twenty-one days in July to November in Fiji, with a mean temperature of 78°—80°, while in November and December with a temperature five degrees higher, complete development was observed on the thirteenth day. Sunder Rao and Iyengar (1930) working in Calcutta are inclined to attach a greater importance to humidity. Monsoon months with high humidity showed heaviest infection, high infestation and increased rate of growth in the mosquito. The optimum temperature was between 85° and 90°. It has been argued that peculiar localisation of the disease is only proportional to the intensity of the distribution of the insect vector, the mosquito; that places which show a heavy infection are breeding grounds for the Culex, where temperature and humidity are favourable for development. Thus, Bahr attributes the coastal distribution in Fiji to the presence of mangrove swamps, which serve as ideal breeding grounds. The association with paddy cultivation emphasized by Korke is also in point.

But is this the whole explanation? A question has been asked and has long remained unanswered. Is there a third phase in the transmission? Is there any truth in the popular belief that infection has something to do with water? Is it possible that infection can occur from contaminated water? Do the infective larvae live in water? Unpublished observations on infective larvae carried out at the King Institute by Menon and Iyer[27] show that, with maturity, the larvae develop a cuticle to resist external conditions. Once this cuticle is formed, the larvae have been found capable of remaining alive in tap water for at least six hours.

Can they make their way from water, penetrate the skin and travel up like hookworm larvae? Is it possible that infective forms, as Manson argued, pass from the proboscis of the mosquito during oviposition or after death and contaminate water? It should be remembered that the actual transmission is not by the bite of the mosquito, but by an indirect transference from the proboscis to the skin of the host. There is nothing impossible in the idea of such a transmission from the mosquito to its breeding swamps and a contamination of the human skin. So far, however, this problem has not been worked out. It is remarkable in this connection, that, in Cochin, the water is so brackish that it is quite unsuitable for drinking purposes. Among the rich, drinking water is brought and stored in casks, while the poorer classes use the water in ponds and low lying drains for drinking and washing purposes. It is among these poorer classes that filariasis is so common.

There are instances in Cochin of a familial and household filariasis. Such cases have been recorded by Burke[28] in Porto Rico. There are also instances of occupational filariasis. Thus filariasis is common in Cochin and Travancore among coir manufacturers, who work their coir in water in low lying areas, before it is made into yarn. Such an occupational incidence is definite among the *dhobies* (washermen) in Saidapet, as pointed out by King, Pandit, Menon and Iyer[29] (1929), in their carefully carried out filarial survey of Saidapet. This frequency, however, they attribute to persistent strain on the lymphatic system of the legs, in those who follow these occupations. On

the other hand, it might be argued that these instances of occupational filariasis are among those who work in water and who come into contact with stagnant water in streams and ditches.

If it could be proved that infective larvae can enter the skin from the water, many of the puzzles regarding the distribution of filariasis would be solved. The hyperendemicity in certain areas and the association with a lack of fresh water supply as noticed in Cochin could be explained as due to the use of infected stagnant water for washing and other household purposes.

In any case it seems that the association between filariasis and a lack of fresh water supply in a place like Cochin is one that is too striking to be ignored. A question of first importance is whether the incidence of filariasis could be reduced with the introduction of a protected water supply. There is some evidence that this is actually the case if we take into account popular beliefs as in Ernakulam and Tanjore that the disease has been much less prevalent with the introduction of river water in pipes. On the other hand, it has been argued that drainage works and general sanitary improvements go hand in hand with a fresh water supply. The intensity of mosquito breeding would then diminish and this might equally account for the lower incidence of filariasis. It might be asked whether the intensity of culicination would sensibly decrease with the introduction of a protected water supply. Culicination in Madras seems to be more marked in areas, where there is an open drainage system, and where these drains are

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ineffective. Houses with large gardens and trees afford protection for the Culex and it is these localities that appear to be specially infested. The problem to be settled is whether filariasis is directly related to the water supply or to an inefficient drainage? This has yet to be determined.

THE PROBLEM OF CLINICAL TYPES.

Another puzzling feature in filariasis has been the relation between the differing clinical types of the disease.

The relation between elephantiasis and filarial disease is now a solved problem. As early as 1891, Maitland[30] argued that this was no more fortuitous association, but that the two conditions were merely differing features of the same disease. He pointed out that many cases of chyluria and lymph scrotum coexist with elephantiasis, that lymph scrotum is followed by elephantiasis of the scrotum and that the same parts of the body are affected and that there is always a history of fever and often of inflammation of the lymphatics. The stumbling block of this theory has been the frequent absence of microfilaria in the blood in cases of elephantiasis. Thus Cruickshank and Wright[19] (1914) found that among 130 cases of elephantiasis in Cochin, only 9·2% showed microfilaria in the blood. Burke[28] (1928) noted in Porto Rico that, out of 59 cases of elephantiasis, none showed microfilaria in the blood. The difference between the microfilaria rate and elephantiasis rate in an endemic focus has been repeatedly noticed by most workers. Maitland

argued that, in such cases, the parent worms were choked and killed in the lymphatic vessels and so, the embryos disappeared from the blood. All access to the blood stream had been cut off. Maitland held that when obstruction was complete elephantiasis resulted, though how the obstruction was brought about was uncertain. This has now been explained. It seems certain that elephantiasis occurs in the late stages of filarial disease when lymphatic obstruction is complete and most of the parent worms are dead or imprisoned within the lymphatics. The recent work on the radiography of elephantiasis has conclusively proved this case.

The variation in clinical types met with in different localities is a problem that requires explanation. Chyluria is more common in India and China while it is almost unknown in the Pacific islands where other types of filariasis are common. In Fiji, Bahr has noted that elephantiasis of the upper extremities is found in 42·6% of cases while it is decidedly rare in India. In South Queensland in Australia, lymphangitis, chyluria and varicose groin glands are common but there is no elephantiasis. Stephens and York[31] have drawn attention to other discrepancies. They mention the great frequency of lymphangiovarix of the scrotum which occurred in 12% of the population in Commoro islands while it is hardly met with in Fiji.

Why is it that elephantiasis is not more common in some places where other types of filarial disease exist? Why is it that it is not found in South

Queensland, is found only in 5% of the population in Cochin while about 50% are affected in the Samoan islands ? Low and Manson Bahr[32] (1920) have brought forward some evidence to explain this. In elephantiasis the embryos are arrested by extensive changes in the main lymphatics or their collaterals and in the distal lymphatic glands they are destroyed. The microfilaria rate is not thus the sole index of the infection of a population. The embryos may be absent in the blood in many cases of chyluria, in filarial abscess and in lymphangitis and yet the parent worms can be demonstrated in the lymphatics. Elephantiasis has been found in places where there is a maximal infection of the population with *Wucheraria bancrofti*. It may be looked upon as 'the expression of massive infection—the parasitic cause is defunct, but the effect on the tissues of the host are permanent'. (Low and Manson Bahr 1920).

It seems reasonable to assume that there are at least three distinct clinical types of the disease, the genital, the upper limb and the lower limb types of filariasis. Sometimes the genital and the lower limb types coexist. Even the genital type itself can be subdivided into at least three distinct entities which have little in common. Elephantiasis of the external genitalia has little relation to hydrocele or to lymphangiovarix of the cord. The lymphatic drainage of the external genitalia is different from that of the testis and the ovary. There is a view that the genital type is due to central lesions either in the preaortic glands or in the receptaculum chyli or in the region of the thoracic

duct and that hydrocele and chylocele represent an overflow of stagnant lymph from the abdominal lymphatics. While it is no doubt true that chylous ascites is the expression of intra-abdominal blockage followed by rupture of the lymphtics, in hydrocele one would naturally presume a blockage low down possibly in the spermatic cord. Just as from recent work, it appears that peripheral lesions in the limbs can be correlated to the presence of the parasites themselves in the peripheral lymphatics, so the frequent presence of the parasites in the tunica albuginea in the speramtic vessels and in the medial sub-inguinal glands may have a more direct bearing on these genital types of filariasis.

There is yet another question. How are we to explain the variation in different localities? Can it be that the infective larvae invade the skin in different areas in differing localities? It is difficult to imagine how the genital lesions can be caused by an entrance through the genital lymphatics unless we presume that the infection is water borne. Are we to agree with Lane[33] (1932) that this is due to the two differing modes of invasion of the larvae, one along the lymphatic stream and the other along the blood? O'Connor's work and our own observations (Bhaskara Menon and Annamalai[31] 1935) have shown the importance of the genitalia in the male as a favourite site of the parent worms in genital filariasis. Do the worms reach the genital lymphatics along the circulatory route while the

peripheral lesions are due to a lymphatic mode of entrance: Or, can it be that there are differing species as put forward by Brug [35] (1927) some favouring the genitals lymphatics and the others, the peripheral vessels?

Recent work has shown that we have, in our midst, a new microfilaria, *Microfilaria malayi,* which has been found in Balasore district in Bihar and also in some areas of North Travancore. This new species, of which the parent worm has not yet been discovered, is smaller and thinner than *Microfilaria bancrofti,* with well marked differences in structure. It resembles to some extent *Microfilaria loa.* This species is also peculiar in that it is transmitted not by the common Culex but by Mansonia mosquitoes, at least as far as we know. Further, Brug has claimed that elephantiasis of the limb type is associated with this species, while *Microfilaria bancrofti* is more commonly associated with the genital type of the disease. These observations have been, to some extent, confirmed by the work of Korke[36] in Bihar and of Iyengar[37] in North Travancore.

While such preponderance of clinical types is observed in endemic foci, hyperendemic areas like Cochin show all the varying clinical types of the disease. Can this be regarded as due to the coexistence of the two different types of the parasite? In a house to house survey of filariasis carried out by King, Pandit, Menon and Iyer (1929) in Saidapet, a focus of high endemicity, all the clinical types were found, with a

predominance of elephantiasis of the legs, as shown from the following figures.

Distribution of filarial disease in Saidapet.

			Males.	Females.
History of fever and lymphangitis only		..	1	1
Enlarged glands alone	.	..	10	6
Enlarged testis or Hydrocele		..	5	nil.
Elephantiasis	Total	..	54	31
do.	Early	..	13	4
do.	Established	..	41	27
do.	arm alone	..	..	1
do.	arm and leg	..	..	1
do.	scrotum alone	..	15	..
do.	legs alone	..	25	29
do.	scrotum and legs	..	14	..
Total number examined		..	847	786
Total filariasis		..	70	38

It is scarcely possible to explain the frequency of the upper limb type in Fiji unless we argue that the mosquito bites the arm more commonly than the leg. Can the preponderance in type be regarded as being due to the differing habits of the affected population? An explanation is possible but this involves the assumption that infection may occur through water.

Acton and Rao [38] (1930) argue that the difference in type is due to the differing intensity of infection. In hyperendemic areas with heavy infection the larvae irritate the first gland they come across with the result that pathological changes occur in the groin glands or the epitrochlear glands; elephantiasis results. With slight infection the larvae are too few to set up irritation low down, but they pass up and the blockage occurs

high up in the aortic group; hydrocele, chyluria and lymphvarix result. In areas of moderate endemicity the irritation and blockage are again high up in the preaortic group; but these are followed later by irritation lower down with continual infection; so hydrocele and other signs of early infection are later on followed by elephantiasis.

This view rests on the assumption that hydrocele, the earliest manifestation of filarial disease is due to obstruction high up; but the question has been raised whether the frequent presence of the worms in the spermatic cord has a more direct bearing on these early genital types of the disease. Our own observations carried out in collaboration with Dr. Sundaresh, Radiologist of the Government Royapuram Hospital show that the worms can be demonstrated in the wall of the sac or within the tunica albuginea in these filarial hydroceles. Extended work however is needed to decide this question.

SYMPTOMLESS FILARIASIS

There are numerous observations that show that infections may occur in endemic areas without well defined symptoms and may be first suspected only by an examination of the night blood. Thus Korke (1928)[39] mentions that 10% of cases in the Gaya district in Bihar showed microfilariae in the blood where filariasis was not suspected on clinical grounds. The microfilaria rate in many hyperendemic foci is much higher than the percentage of population showing obvious clinical features of filariasis. This symptomless

filariasis has been the subject of much comment. Does it mean that the sheathed microfilariae are themselves harmless and incapable of giving rise to lesions? The presence of embryos in the blood presupposes parent worms in the lymphatics. The question is intimately bound up with the pathogenicity of the parasites. The view has been put forward that the parent worms are themselves innocuous and that the pathological effects are due mostly to complicating microbic invasions. On the other hand, Low and Manson Bahr[40] (1928) argue that ' statements to the effect that perfect health of the human host may coexist with filarial infection, have frequently been made, but if the after history of such cases is systematically followed up, more often than at present, it would be found that sooner or later many would develop pathological signs of definite lymph stasis '. This has been their experience both in the West Indies and in Fiji. The recent researches of O'Connor and his colleague have shown that hyper-filariation originally suspected by Manson actually exists in hyperendemic foci. The small size of the parent worms makes them difficult to find in diseased tissues unless serial sections are carried out. Patho-logical effects depend to a great extent on the dose of the infecting worms. If the infection is slight and if a few worms are only present the lesions are not wide spread and clinical features might be slight; an obscure enlargement of a lymph node might be easily overlooked and a single attack of filarial fever might be attributed to some other factor. The discovery of a favourite site of the parent worms in the lymphatics of the testis and

the lymph plexus of the spermatic cord has demonstrated that, in many cases, more worms are present than are actually found in pathological examinations. Symptomless filariasis may therefore be looked upon as an instance of parasitism similar to symptomless hookworm disease or amoebiasis—where the parasites are present but the pathological effects are slight depending on the dosage. It is doubtful, however, though biologists might incline to this view, that a state of harmony might arise between a protozoan or metazoan pathogen and the human host. Clinical sympomatology is largely dependent on the acuteness of the clinician and the intelligence of the patient. The pathological effects are there, but they require careful and prolonged observation for their elucidation. Further, it must be remembered that obstruction must be advanced and in multiple foci before clinical signs appear. The anatomy of the lymphatic system with its numerous collateral channels of drainage would render a slight focal infection, due to one or two worms, unnoticeable. For well marked pathological effects a high filariation is essential, since multiple blockage seems necessary to show up the lymph stasis.

Symptomless filariasis is thus an expression of a mild infection where the lymphatic blockage is slight and almost unnoticeable; clinical filariasis will be the expression of a more severe infection, a larger dose where obstructive lesions are more apparent, while in elephantiasis we have the end result of a chronic and extensive lymphatic blockage, of a maximal filariation, where the lymphatics of the human host form a living
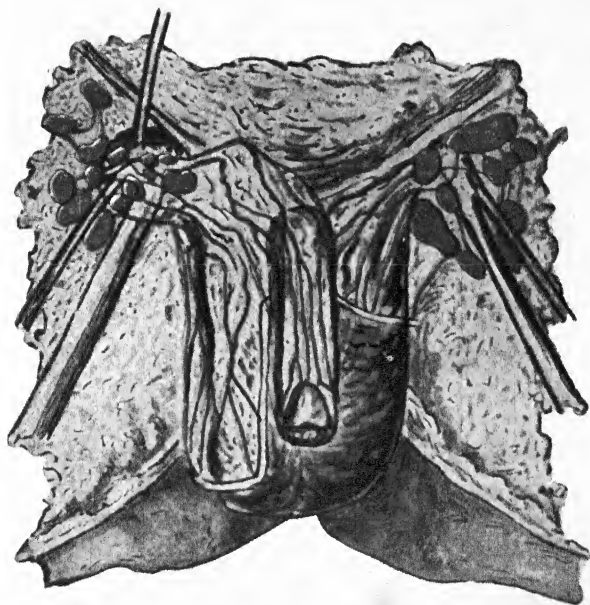
cemetery where the parasites both dead and alive are entombed.

THE GAP IN THE LIFE CYCLE.

As pointed out by Sir Frank Connor [41] a gap in the life cycle, to which little attention has been paid, is regarding the fate of the infective larvae after leaving the proboscis of the mosquito. We next find the parent worms in the larger lymphatics; some are in the peripheral lymphatics of the lower limbs, others in the afferent sinuses of the lymph glands, others in the abdominal preaortic groups and more often than was originally suspected, in the lymphatics of the testis and spermatic cord. What determines the location of the mature worms and how do they reach the central lymphatics? Following the bite of the mosquito, one would suppose that, along the lymphatic stream, the infective larvae would settle in the large lymphatics of the limbs or in the afferent sinuses of the regional glands. If, on the other hand, we assume that there is some instinct that guides the worms towards the central lymphatics, we should invariably find the preaortic groups most often involved. Yet enlarged epitrochlear glands are commonly met with as an early feature of infection in Fiji and a similar involvement of the sub inguinal group is common. Do the larvae mature in the small peripheral lymphatic vessels or the medium sized or the large lymphatics. Do they even reach maturity at the site of entrance? These questions have yet to be settled.

How are the deep lymphatics of the spermatic cord and testis affected? Genital bites from mosquitoes are

far from common; even if this were so, the subinguinal glands are the ones that drain the external genitalia. How are we to explain the frequent presence of the worms in the spermatic cord and the tunica albuginea, as recorded by Shibutani[42] (1917), Watanabi [43] (1929), Scrour[44] (1929), Ray[45] (1934) and other numerous observers. Lane[46] argues that the larvae may enter either through the lymph escalator or the blood escalator; their maturation in the genital lymphatics, Lane regards as due to an instinctive migration from the vascular system to the large lymphatic plexus, surrounding the vas. If this were so, why does this instinctive migration occur only in male? A filarial salpingo-oophoritis, pathologically proved, is hardly met with and there are no records to show that the worms ever seek shelter in the uterine lymphatics. Here the lymphatic vessels are large with numerous ramifications which can afford as much shelter as the lymph plexus of the testis. On the other hand, elephantiasis of the external genitalia in the female is far from uncommon. This difference in the distribution of genital lesions in the male and the female, does it not suggest that the simplest route is the one that is followed and that the sex differences of genital filariasis are due to simple anatomical facts? If we are to assume that the larvae can enter from the skin of the external genitalia, then depending on the degree of penetration one would find simple effusions into the tunica vaginalis, epididymo-orchitis, nodules in the spermatic cord and funiculitis. Lastly, as the result of persistent

Superficial lymphatic vessels of penis and scrotum and
inguinal glands (after Bruhns.)

and continual infection, elephantiasis of the genitalia of the male or female would result from multiple blockage of the regional glands. The internal genitalia of the female, as distinct from the male, are all in the abdominal cavity and far away from the larvae on the skin. They can only be involved either by a verminous descent from the preaortic group which would mean a retrograde passage against the lymphatic stream or according to the view of Lane by an instinctive migration from the blood. This is a problem that requires explanation.

THE PROBLEM OF MICROFILARIAL PERIODICITY.

The remarkable phenomenon of the periodic flooding of the blood with filarial embryos has been one of the most baffling problems in tropical medicine. The periodicity is nocturnal with *Microfilaria bancrofti,* but there are other microfilariae that exhibit diurnal periodicity. Still more puzzling is the lack of periodicity observed with forms apparently identical with *Microfilaria bancrofti* in certain localities. Thus Bahr (1912)[47] found a lack of periodicity with *Microfilaria bancrofti* in the Samoan islands; while Buxton[48] points out that it is remarkable that in the neighbouring group —New Hebrides—there is nocturnal periodicity even though *Acdes variegatus* is apparently the vector. Fülleborn[49], (1912) observed nocturnal periodicity in German New Guinea and the Bismarck archipelago but no periodicity was observed in the Samoan troops in Hamburg. No differences in morphology could be found in the microfilariae exhibiting these variations. Nocturnal periodicity begins about six o'clock in the evening and the embryos reach their maximal concentration at about midnight. During the day, the microfilariae disappear from the blood or can be seen only in very scanty numbers. This filarial periodicity is constant and can be seen in the same patient from day to day. What is the explanation of this remarkable phenomenon? Manson[50] (1899) held that, during the day, the embryos disappeared into the lungs, the great

vessels of the thorax and the heart. Evidence for this view was from the post mortem findings of Young[51] (1897) in the case of a negro under Manson's care. He had come to London seeking relief for two large semifluctuating swellings due to dilated lymphatics in the groins. He had microfilariae in the blood showing nocturnal periodicity. One morning, about 8 o'clock, he committed suicide by swallowing prussic acid. Death was instantaneous. At the autopsy which was held at 2 p.m., it was found that no microfilariae were present in the peripheral blood, in the liver or the spleen but they were, almost all in the pulmonary capillaries, some in the great vessels of the thorax and in the heart. Similar autopsy findings are recorded by Low[52] (1931) in a negro, and by Fülleborn in a Chinese. Manson held that this disappearance was not due to quotidian parturition since fluid in lymphorrhagia showed a constant stream of the embryos. How they maintain their position in the blood current in the great vessels during the day was unknown. What is the explanation of this singular migration was the next question. Manson held that the nocturnal appearance in the blood was an adaptation to the feeding habits of the intermediary host, the mosquito.

Thorpe's[53] view that the periodicity was dependent on the hours of the sleep of the patient was, to some extent, confirmed by the experiments of Stephen Mackenzie[54] (1882) who showed that the periodicity was gradually altered by making the patient sleep during the day. Yet the appearance of the embryos begins some hours before the sleeping state.

Relaxation of the capillaries is the reason why the embryos enter the peripheral circulation according to von Listow[55] (1892).

The retention theory of Smith and Rivas[56] (1914) is based on the passivity of the sheathed microfilariae, which are unable to pass through the narrow capillary bed to the venous circulation without the pumping action of the heart aided by movement, external stimuli and muscular activity. When these are diminished during sleep, the embryos are *retained* in the peripheral capillaries. The periodicity is only relative depending on the amount of blood examined. The periodicity of the *Microfilaria loa* is diurnal, because the parent worm lives in the subcutaneous tissues and the embryos have to work their way up through the lymphatic system. Here there is practically little circulation during sleep. *Microfilariae loa* thus enter the blood stream during the day but they are held up in the capillaries of the lung during the night. Diurnal periodicity is found only in long standing infections while early infections show only a lack of periodicity. The other small unsheated microfilariae show no periodicity because they can actively wriggle through the capillaries.

Fülleborn[57] held that the periodicity was not due to passive retention in the lung capillaries, but that the periodic microfilariae took up a bent attitude during the day and this posture was responsible for their retention in the lung.

Clayton Lane[58] (1929) has raised the question whether the periodicity is due to cyclical parturition

during the day.   This theory, first suggested by Myers[59] (1881) was rejected by Manson since there was no evidence that the embryos died during the day.   They could be kept alive for days together " in vitro ".   Lane argues that the periodicity can be explained by only one of two mechanisms, either that the embryos retired to some remote haunts during the day or that they are destroyed every day.   So far no such diurnal reservoir has been demonstrated.   The classical post mortem on Manson's case, it is true, showed marked concentration of the embryos in the lung capillaries and in the thoracic vessels but Anderson's (1929) post mortems[60] on two cases, one where death occurred during the day and the other at night, showed no marked difference in the concentration of the embryos in the lung.   It is difficult to imagine how the sheathed microfilaria can remain in 'the Niagra' of the aortic blood.   Lane is inclined to regard their presence in the thoracic vessels as due to post mortem migration of the embryos liberated from the female in the large lymphatics.   Lane further cites Fülleborn's result of recovering enormous numbers from puncture of the heart after death, while puncture during life showed only the same concentration as in the blood.   Manson and also Myers had negative results from puncture of the spleen and the liver.   Lane, therefore, rejects the theory of a diurnal reservoir, and regards the periodicity as due to a simultaneous cyclical parturition of the females living in the lymphatic vessels.   Lane argues that the parturition of the mature females is *simultaneous.* O'Connor and Hulse[61] (1932) have recently brought

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forward some evidence in support of this view. They have found many worms in the same stage of embryo development—in glands removed at one time—and they has also found a twelve hour gap between parturition and the swarming of embryos in the blood in Porto Rico. Lane explains this twelve hour gap as due to the period taken by the embryos in travelling up the slow lymphatic current from the glands to the thoracic duct and up the duct to the circulation. This 'lymph escalator' of Lane is a slow moving and tortuous passage which finally lands the embryos in the blood, hours after they are liberated by the female worm. Dr. Annamalai and I have also some evidence in support of this view. In one case, in a lymphatic vessel in the tunica albuginea of the testis, we found three female worms and one male. All the worms were well preserved showing that death was quite recent. In all the three females, the posterior ends of the worms were crammed with ova, while the anterior portions were filled with embryos and parturition seemed imminent. The presence of three females, all showing embryos, seem to show that parturition is much more frequent than was thought of before. In another case the patient was admitted with painful diffuse swelling in the spermatic cord extending down to the testis. This was suspected at first to be a strangulated hernia. Operation was done at about 2 p.m. at the General Hospital, Madras. The histological section of the cord showed one female worm in a lymphatic vessel in the cord. The worm was lying in a little clear fluid and the histological structure suggested that it was alive. The uterine tubes were

quite well preserved and showed ova instead of embryos. Can one assume here with Lane that parturition had already taken place since no embryos were found? Lane explains the non-periodic types as varieties where parturition of the females is not simultaneous and synchronous but irregular in the 24 hour cycle.

A serious objection to this theory has been the lack of evidence regarding the fate of the microfilariae. These have been found to live in artificial culture for over a month. The forms in the blood show no degenerative changes due to age. Where are they destroyed and why is it that their destruction, if it occurs every day, is not followed by tissue reactions as in the malarial crisis? There is no evidence that, the spleen which deals with the malarial parasite, is specially concerned. Do the microfilariae wander back to the lymphatic glands? O'Connor[62] (1932) has brought forward definite evidence that microfilariae are destroyed in the body in the lymphoid tissues. Calcifying microfilariae have been demonstrated in numbers in the lymphatics of the tunica vaginalis. Sections show living and dead microfilariae in the polypoid formations in the walls of the larger lymphatics. If cyclical destruction is an every day event in the lymphatic tissues, we must look for more evidence of lymphoid reactions in filariasis. Is there any evidence that they are destroyed in the vascular system? Bahr has found that they are destroyed at *body temperature* in citrated blood in vitro, while at room temperature it is well known that they can remain alive for days. The experimental evidence for the destruction in the blood is still uncertain.

Rodenwaldt[63] (1908) and also Fülleborn have observed massive destruction in the kidney, but these results have not yet been confirmed. On the whole, Lane's theory rests on the demonstration of a burial ground where the microfilarial broods in the blood are disposed of every day. This has yet to be carried out.

Low and Manson Bahr[64] (1934) have criticised this theory. In a case, where the microfilarial counts were observed from day to day for weeks together, the total count on twenty-four hours was more or less constant. On Lane's theory this would mean that the fresh broods that are born every day would consist of similar numbers of microfilariae. They argue that heavy blood infection of embryos cannot be correlated with the severity of lymphatic obstruction. If embryos are destroyed in such large numbers in the glands, signs of lymph stasis must be in proportion to the microfilariae in the blood. Lane's argument of post mortem migration of the embryos, they think, as unlikely since the circulation would have stopped after death. They hold that the periodicity is in some way related to the habits of the human host, since a repetition of Stephen Mackenzie's experiment was followed by an irregular periodicity.

On the other hand, Lane[65] (1934) in a recent paper has brought evidence to show that a post mortem flow of lymph does occur at least in cyanide poisoning. He argues that a microfilarial spicule which could fix the embryos in the large vessels has not been demonstrated. He holds that degenerative changes due to age have been demonstrated in the careful studies of O'Connor.

Can it be that parturition is not a daily event? Has the noted periodicity of the attacks of filarial fever anything to do with a periodic parturition once a month? What happens to the microfilariae after they swarm in the blood if they are not destroyed. Do they wander back to the lymphoid tissues which are the site of predilection for the worms? Can the sheathed embryos flow back into the lymphatic spaces? If this be so the periodicity would then be due to the alternation of two cycles, one in the blood stream and the other in the lymphatic system.

It is interesting to note in this connection, that O'Connor[66] (1923) has attributed the non-periodic forms to the transmission by another intermediary host *Aedes vaiegatus var. pseudo-scutellaris* which bites both during the day and night. *Culex fatigans,* the transmitter of the periodic form is a night feeder. The diurnal periodicity of Loa loa is regarded as dependent on the intermediate host, a fly *Chrysops dimidata* which is a day feeder. If cyclical parturition is the cause of microfilarial periodicity, it would mean that all the female worms, owing to some unknown stimulus, adopt their parturition to a biological period that is essential for the continuance of the life cycle. What is the stimulus that determines this cyclical parturition? Harley[67] has put forward a theory that the saliva of the insect host might act as a stimulus. A positive chemiotactic effect of this foreign protein might draw the microfilariae towards the regional glands involved, where they may be destroyed. Harley argues that the

stimulus for cyclical parturition of the female worms may be this same foreign protein from the mosquito's saliva, which may set up uterine changes.

PATHOLOGICAL PROBLEMS.

The essential lesions met with in filariasis are the lymphangitis and the obstructive lesions resulting in lymphangiectasis and elephantiasis. Just as there is a good deal of controversy regarding the filarial origin of the lymphangitis, no agreement has been reached with regard to the obstructive lesions met with in filariasis, as to whether they are due to the presence of parasites' in the lymphatics, whether they are the end results of secondary septic lymphangitis or whether they are due to changes in the glands from the passage of the infective larvae. Mechanical blockage with ova, from abortion of the worm, as postulated by Manson is only a speculative view.

The nature of the lymphangitis.—

In most cases of filarial disease, there is, from the commencement, a history of recurring attacks of fever and painful adenitis in some part of the body. The association between focal tender areas and febrile attacks has been noted even from the time of Sushruta and Mādhavakara. Occasionally, in hyperendemic areas, cases are encountered, without a definite history of febrile attacks. While inguinal adenitis is common, in many cases as noted by O'Connor[68] (1929) only focal painful and tender spots in the skin and subcutaneous tissues are metwith. These are often attributed to mosquito bites; but, in cases, I have personally observed the recurring attacks seem to commence with pain and

tenderness at the same or neighbouring spots. The spreading lymphangitis appears clinically as fine irregular pinkish red lines that more or less converge towards the swollen and tender spot. While most often, the skin of the legs is affected, in some cases the arms are involved, while, in old cases, the attacks are referred to definite areas, orchitis, epididymitis, inguinal adenitis etc. Cruickshank and Wright[69] have classified their cases in Cochin into

> (1) Fever with pain in the groins.
> (2) Fever with pain in the arms.
> (3) Fever with rigor which is not malarial.

A periodicity of these attacks has been described by Bird[70] (1916) and also by O'Connor (1929), and from personal experience in Cochin, I can fully confirm these observations. The patients very often give a history that these attacks come on once a month almost with cyclic regularity. The attacks gradually disappear when the patient leaves the endemic focus. A seasonal fluctuation in such cases has also been recorded by Martinez[71] (1916) in Porto Rico.

With regard to the blood changes in lymphangitis, a polynuclear leucocytosis and a post-febrile nocturnal eosinophilia have been noted by Martinez (1916). Rose[72] (1919) has also drawn attention to the leucocyte picture with the shift to the left, of the Arneth index, which he regards as suggestive of a septic process. O'Connor (1932), however, regards this polynuclear leucocytosis as a transitory phase while a lymphocytosis is the important feature. The frequent disappearance

of the embryos, from the blood, after the attack of lymphangitis, is a feature of great significance. Bahr has observed this in seven out of nine of his cases in Fiji and similar results are recorded by O'Connor.

The anatomy of the lymphatic system.—

The lymphatic system is now regarded as a system of closed vessels which are distinct from the spaces or crevices in tissues which were formerly looked upon as lymph spaces. There is evidence, however, that this system of closed tubes is in easy communication with the tissue spaces permitting the transference of fluid. The lymph capillaries are the smallest tubes of the lymphatic system. They form a superficial mesh-work, just under the skin, which communicates with larger vessels of a similar type in the subcutaneous and deeper tissues. From this capillary plexus, the lymphatic vessels arise. These are tubes more or less similar to veins in structure in having valves and three coats in their walls. They vary in calibre and form larger trunks which gradually pass towards the lymphatic ducts—the thoracic and right lymphatic duct, from which the lymph is drained into the circulation. The lymphatic glands appear as nodes of thickening along the course of the lymphatic vessels and serve as filters of the lymphatic system.

Histological changes in the lymphatics.—

The lymphangitis in filarial disease makes its appearance in the medium sized lymphatic vessels which show up as fine red lines on the skin when they are inflamed. The extension to the more superficial
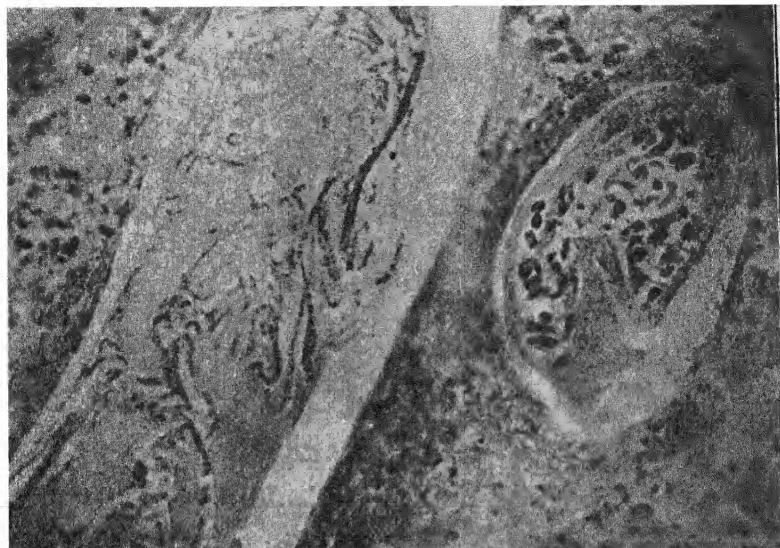
vessels appears as a later event. Histological studies suggest that the inflammation begins in the lymphatic vessels in which the parent worms are present. This can be demonstrated by serial sections in cases where the worms are found inside a lymphatic vessel. A spread of infection from the capillaries of the skin to the deeper lymphatics is a possible mode of origin, but is not usual.

In the medium sized lymphatic vessels, the histological changes vary. Irregular inflammatory masses of tissue project into the vessel, forming a type of endolymphangitis polyposa. These polyps are composed mostly, of subendothelial tissue which shows lymphoid clusters, somewhat resembling the lymphoid granulation tissue met with in syphilitic endarteritis. The endolymphangitis may be so marked that the lumen of the affected vessel may be obstructed, an obliterative endolymphangitis. Perilymphangitis is also met with and in some cases, the whole wall is diffusely infiltrated. While slight changes are the rule round healthy worms as shown in microphotograph, marked changes with, complete obliteration of the lumen are met with round dead and disintegrating worms, as shown in microphotograph(7). Here we have a longitudinal section of an affected lymphatic containing a dead worm. The inflammatory infiltration of the wall is so marked that it is difficult to distinguish the vessel unless one follows up the thin layer of plain muscle in the middle coat. Around dead and disintegrating worms, this reaction extends all along the length of the worm so that the whole parasite is enclosed in a case or core of inflamma-
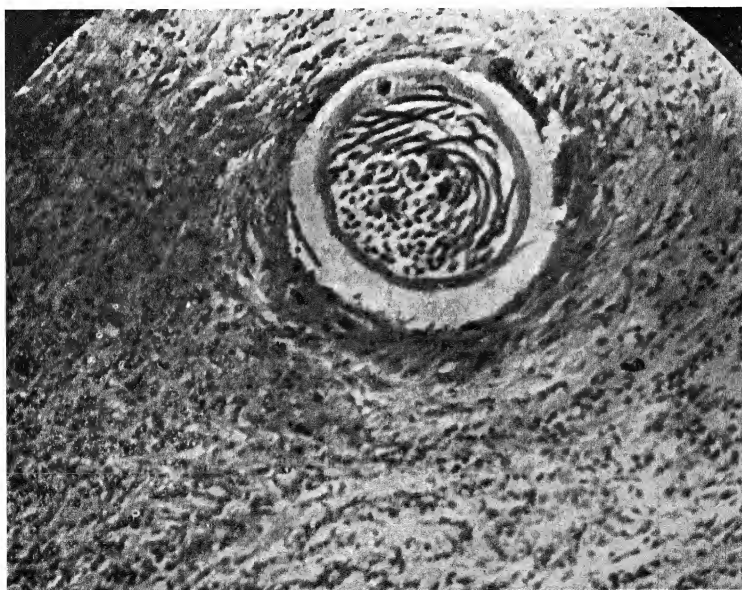
tory tissue inside the affected lymphatic vessel.
Inflammatory changes round the small lymph capillaries are not common, but such changes are best seen in elephantiasis. With regard to the site of the lymphangitis, the limbs are most commonly affected but the conditions most often described as endemic funiculitis, epididymo-orchitis seem to me to be merely expressions of the same lymphatic inflammation, as they affect the vessels of the cord and the testis.

The Acute Eosinophilic inflammation.—

While varying grades of endolymphangitis are met with in filarial disease, showing a resemblance to other types of lymphatic inflammation, the distinctive feature is the type of the histological reaction around the lymphatic vessels. This reaction consists of an eosinophilic emigration and the pouring out of an inflammatory exudate which shows varying degrees of coagulation necrosis. Attention has been drawn to the eosinophilia round the worms by Bahr (1912), by Shibutani (1917), by Serour (1927) and recently by O'Connor and Hulse (1932). This reaction is most marked around the anterior end of the parasite (Bhaskara Menon and Annamalai 1935),[73] as shown in microphotograph (1). The concentration of cells might be so marked as to suggest *an eosinophilic abscess.* In other cases, the eosinophilia is diffuse, the cells are separated by an inflammatory oedema, with here and there clusters of lymphoid cells and plasma cells. The whole reaction is distinctive and unlike anything met with in pyogenic inflammations and is well illustrated in a slide of acute filarial orchitis as shown in microphotograph 5 (b).

Photomicrograph I. High power view of a female worm showing the body distended with embryos and a cross sowing ova. The body is well preserved showing that death had been recent. Note the necrotic coagulation and the clusters of eosinophiles round the worm. (x 500)
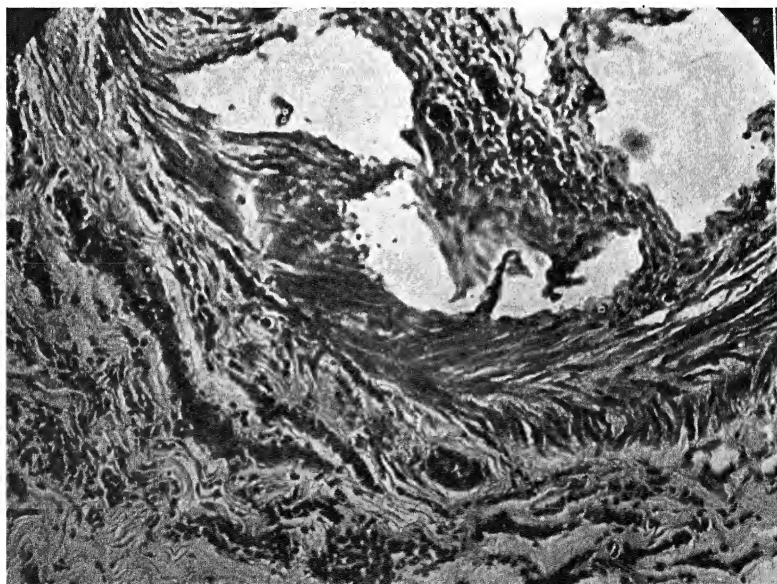

Photomicrograph II of a female filaria showing embryos. Parturition has not yet taken place (Case II). Two other female worms are found in the same stage. (x 500)
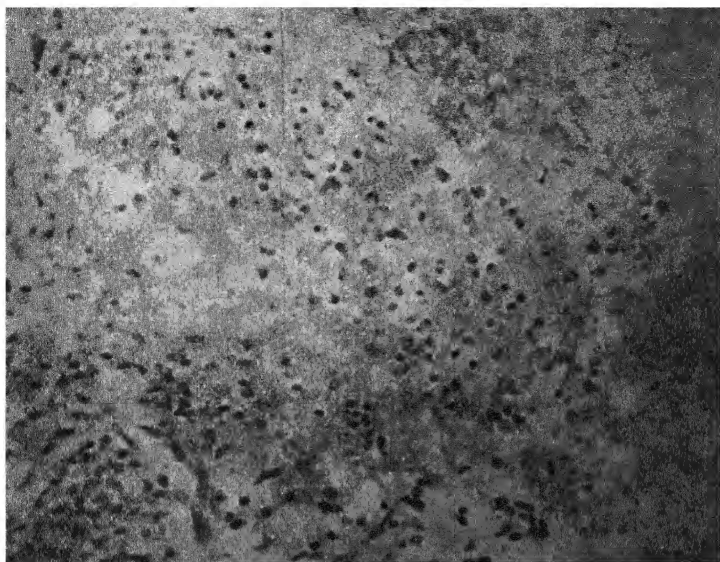
Photomicrograph III showing healthy female worm in a lymphatic vessel. Note the body is filled with ova and not embryos. There is a polypoid endo-endolymphangitis. (x 50)
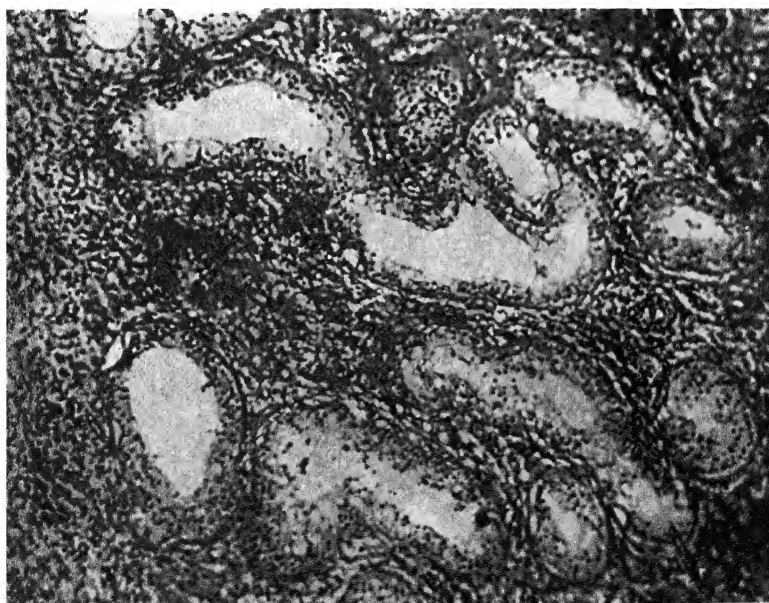

Photomicrograph IV showing endolymphangitis obliterans in a large lymphatic vessel with a hypertrophied muscular coat. (x 310)

Photomicrograph V. A. Inflammatory tissue. Acute eosinophilic inflammation. Note the concentration of bilobed eosinophiles and mononuclears. Polymorphonuclear cells are absent. (x 310)
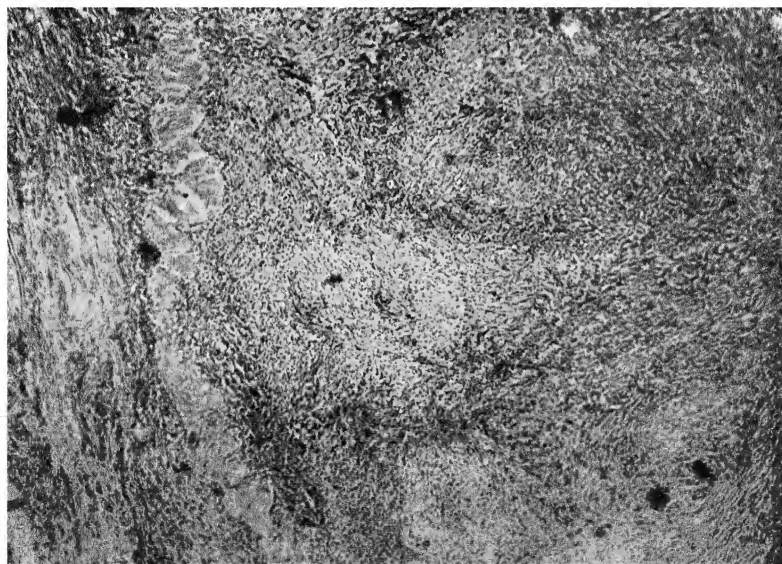

Photomicrograph V. B. Acute diffuse orchitis with inflammatory oedema of the intertubular tissue and infiltration with clusters of eosinophile cells—acute eosinophilic orchitis in filariasis. (x 50)

Photomicrograph VI. Filarial pseudo-tubercle. Note the **foreign body** reaction and tubercle formation round the tail end of a female worm. There is a large foreign body giant cell. (x 50)
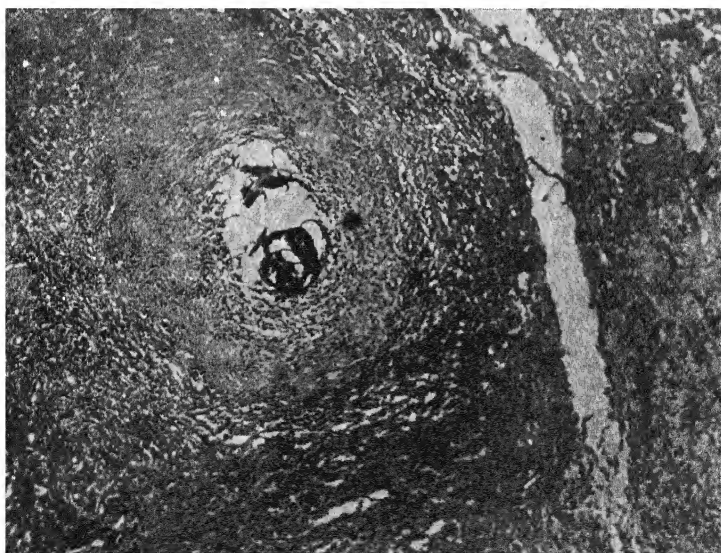

Photomicrograph, VII, showing the filarial granuloma. Note the muscle coat in the wall of the lymphatic vessel. The lumen is almost blocked up by an inflammatory mass which has formed around the parasites. (x 16)
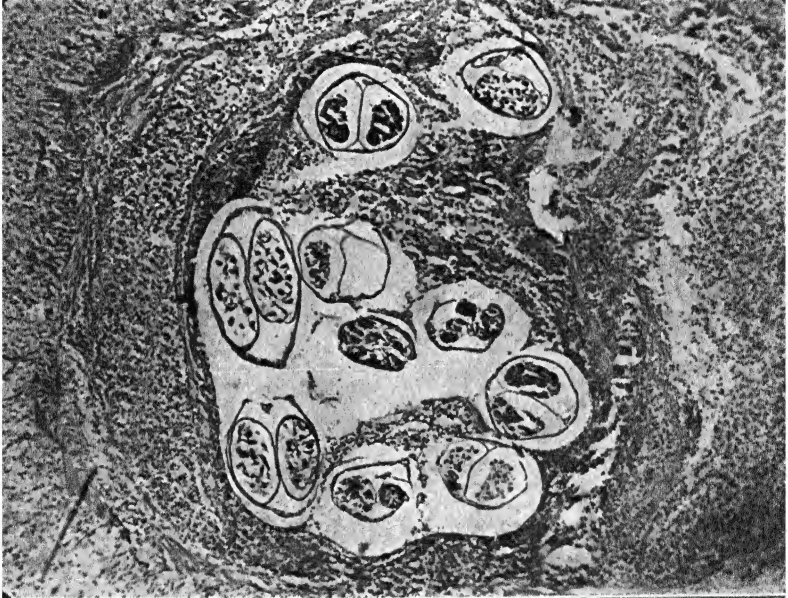
Photomicrograph VIII. Filarial granuloma. Reaction round a male worm. Not the cluster of endotheloid cells that form a tube like case around the parasite. Note that the body of the worm is well preserved and contains no uterine tubes. (x 50)

Photomicrograph IX showing fragments of a dead female worm in the process of encapsulation and absorbtion. (x 50)

Photomicrograph X showing the change in type of the inflammatory reaction round the worm with septic infection. The worms are lying in the lumen of a lymphatic vessel filled with pus. Note the clusters of disintegrating polymorphonuclear cells. (x 50)

Occasionally cases are met with, where the affected lymphatic is acutely inflamed round a disintegrating worm which is lying in a mass of dead and breaking down polynuclear cells, suggesting that suppuration has taken place round a dead worm. (microphotograph 10).

The filarial granuloma; the filarial pseudo-tubercle.—

Another type of inflammatory change that is found round the worms lying in the lymphatic vessels is more chronic in type and resembles the formation of tubercle follicles in infections with *B.tuberculosis.* The term ' filarial granuloma ' has been applied to this condition by Ku and Kao[71] (1924). This type of reaction is well known from the descriptions of Bahr in Fiji and of Cruickshank and Wright in Cochin. It is more of the nature of a foreign body reaction round remnants of the dead worms during the process of absorption or calcification. In cases observed by us, (Bhaskara Menon and Annamalai 1935), we have noticed that the reaction very often occurs at the posterior end of the parasite. Gradually the whole body of the worm becomes surrounded by a tubular mass of pale staining endothelioid cells, as in the tubercle follicle. Some of these endotheloid cells apparently fuse together and send protoplasmic filaments which arborise round the cuticle of the dead worm. Large syncytial cell masses are thus formed. These are practically indistinguishable from foreign body giant cells. Lymphoid clusters are generally present at the periphery and the whole appearance suggests a pseudo-tubercle. (photomicrograph 6). Calcification either in fine lines or in irregular granules may be met with in the body of the

worm but the chronic reaction described above is met with long before calcification occurs. Encapsulation and fibrosis are also met with as late reactions where the fragments of the parasites are mostly absorbed or have undergone calcification. In microphotograph 9, the dead worms are lying in a lymphatic vessel, the wall of which is completely fibrosed and the lumen is much narrowed. Caseation necrosis is not met with.

The cause of the Lymphangitis.—

The exact mechanism of production of the lymphatic inflammation has not yet been settled. The occurrence of lymphangitis in infections of the skin and in surgical sepsis and the clinical similarity of such cases to tropical lymphangitis met with in filariasis, no doubt attracted attention, and as early as 1892 Sabouraud[75] described typical attacks in non-tropical elephantiasis due to the presence of bacteria in the tissues. The finding of bacteria in filarial abscesses raised the question of complicating bacterial infections and their part in the lymphangitis. This view was first put forward by Prout[76] (1908) who held that the lymphangitis was essentially bacterial. Subsequently, opinion has been divided with regard to the role of bacteria in filariasis. Bahr's studies in Fiji failed to prove a microbic factor in the lymphangitis. He recovered staphylococci from pus from filarial abscesses, but fluid from lymphangitis was sterile. Similar results were obtained by Cruickshank and Wright (1914). On the other hand, the studies of Wise and Minnet[77] (1913) in British Guiana again drew pointed attention to the coccal infections in filarial abscesses. The finding of a

bacillus by Dutcher and Whitmarsh[78] (1915) in the blood in filarial lymphangitis has not been subsequently confirmed. Rose[79] (1915) again drew attention to the finding of streptococci in fluid from filarial glands, and in subsequent work published results of the success of streptococcal vaccines in the treatment of filariasis. The frequent finding of streptococci and staphylococci in filarial abscesses in British Guiana was emphasized by Anderson so that the British Guiana Filarial Commission (Anderson[80] 1924) came to the conclusion that the lymphangitis was essentially due to secondary pyogenic infections.

Grace and Grace[81] (1931) in their recent researches in British Guiana have recorded their finding of haemolytic streptococci in abscesses and elephantoid tissues, but their work has been criticised on the ground that evidence of the filarial nature of these cases has not been brought forward. In Porto Rico, Saurez[82] has demonstrated the presence of bacteria in the lymphangitis but extensive studies by McKinley[83] (1931) in 38 cases showed no growth in 27 cases where material was aspirated from the deeper tissues at the site of inflammation. Of 11 cases, when material was obtained from the skin over the inflamed part, three showed growth. On the other hand, in 9 cases of filarial abscesses, 7 showed streptococcus haemolyticus and two staphylococcus aureus. McKinley concludes that the real filarial lymphangitis is bacteriologically negative, but that there are cases of septic lymphangitis that simulate the condition and are due to pyogenic cocci. O'Connor supports this view. On the other

hand, Grace[84] (1934) maintains that filarial lymphangitis is a mild erysipelas produced by a special strain of β haemolytic streptococcus of low virulence probably residing in the skin; he holds that the role of the parent worms in the production of these attacks has not been demonstrated; that, in fact, filarial lymphangitis is not filarial, but streptococcal.

In India, the microbic theory of the lymphangitis has received extensive support from the work of Acton and Sunder Rao[85 & 86] (1929 & 1930). They hold that there are two types of lymphangitis, one toxic, from toxins produced by the worms and the other, bacterial most often due to streptococcus haemolyticus. The streptococci may enter the tissues from any area of focal sepsis; that a local failure of the defense mechanism, a kataphylaxia, either epiblastic, mesoblastic or hypoblastic would favour the entrance of bacteria. On the other hand in Giglioli's[87] attempts to induce fixation abscess in filarial lymphangitis, the abscess remained sterile.

Our own histological studies (Bhaskara Menon and Annamalai 1935) and those of O'Connor and Hulse (1932) tend to show that definite pathological changes occur in the lymphatic vessels round the worms during death; that there is, in these cases, an obstructive endolymphangitis and so far as histological evidence goes, this is the main type of the lesion that has been demonstrated up till now. It must be emphasized that changes round the dead worms have been originally described by Bahr in Fiji (1913) and also by Cruickshank and Wright in Cochin (1914) and this, no doubt, led to the view of verminous responsibility for

the lesions in filariasis. In our own studies, we have found, in addition, an acute eosinophilic inflammation round the dead worm that is distinct from the chronic encapsulating reactions which occur at a later stage. This acute eosinophilia with a coagulating exudate is an early reaction round worms where death is imminent and is quite different from the absorption of the dead worm. There is nothing to suggest any similarity to a pyogenic and bacterial inflammation.

On the other hand, it must be understood, that cases occur where, from complicating microbic infections, there is a change in type of the inflammatory reaction to a polynuclear and suppurative lymphangitis, as in a case we have described. De[88] (1934) has also brought forward post-mortem evidence of streptococcal septi-caemia complicating three of his cases in Calcutta. It is also significant, in this connection, that most of the positive bacteriological findings are in cases of filarial abscesses, where it is possible that secondary bacterial invasion has taken place, though, in a number of instances, these abscesses have been found to be sterile.

Much importance has been attached to the polynu-clear leucocytosis during the lymphangitis, as indica-tive of bacterial infection. This might equally be so with a toxic process. Besides, O'Connor has pointed out that this leucocytosis is only transient and is followed by a lymphocytosis which is the essential change.

Another theory regarding the causation of the lymphangitis is that these attacks are due to the parturition of the worms. Parturition, it is argued, is

attended with some toxic discharge which is responsible for the inflammation. The periodic discharge of microfilariae, about once a month, is thus held responsible for the periodicity of the lymphangitis. Bahr's case of recurring orchitis is in point, if orchitis is looked upon as a lymphangitis of the testis. He has recorded a case with alternating attacks affecting each testis. Fluid collected in the tunica vaginalis on each side with swelling of the affected testis. Microfilariae were demonstrated in the fluid on each side with repeated attacks.

Filarial lymphadenitis.—

The swelling and tenderness of the regional lymphatic glands make their appearance with the attack of lymphangitis, but very often persist, even while the lymphangitis disappears. With repeated attacks, the glands become very much enlarged and fibrosed. Sometimes they attain enormous dimensions as in the illustrations figured by Bahr in Fiji. The histological changes in the glands consist, in the beginning, of a catarrh affecting the cortical sinuses, followed by a gradual atrophy of the lymphoid elements. O'Connor and Hulse (1932) have demonstrated changes in the afferent sinuses of the gland round parent worms. They hold that the efferent sinuses are free. Bahr has also demonstrated changes round adult worms in the gland. He argues that the fibrosis and the enlargement of the glands are directly due to the presence of the parent worms. Changes in the gland round microfilariae have also been demonstrated. Calcified and disintegrating microfilariae have been found. Occasionally

eosinophilia in the gland has been noticed. In long standing cases with enlargement, the glandular tissue is more or less replaced by large bands of fibrous tissue. On the whole, histological studies of the lymphatic glands are so few, that it is not possible to decide whether the changes could be directly attributed to toxic and foreign body reactions round the parent worms or whether the reaction is due to a toxic discharge from the worms lying at some distance from the glands. In this connection, Acton and Rao[89] (1930) have advanced an interesting theory that the changes in the glands are due to the irritation caused by the infective larvae, in their passage from the site of entry into the deeper lymphatics. They hold that the lymphadenitis varies in type with the dosage of the infective larvae, that with minimal infections, subacute lymphadenitis with slight swelling of the juxta-aortic glands results, while in heavy infections in hyperendemic areas, there is a marked chronic lymphadenitis with enlargement and fibrosis of the glands low down. However, more histological evidence with the actual demonstration of the larvae in the gland is essential to settle this question.

Obstructive lesions.—

It is easy to understand how obstruction occurs in the lymphatic system. With recurring attacks of obliterative lymphangitis and fibrosing lymphadenitis, some of the lymphatic channels are blocked, and lymphangiectasis, a dilatation and varicosity of the lymphatic vessel, makes its appearance. This is more marked when the obstruction is more complete. It is

L—6

also easy to realise why signs of lymph stasis are very often absent in mild infections, since the lymphatic vessels have numerous collaterals which carry on the circulation. Blockage high up where the lymph vessels converge or blockage in regional glands and especially blockage near the thoracic duct is most often followed by lymphangiectasis. In lymphangiectasis, the vessels become not only dilated, but the walls undergo true hypertrophy so that the enlarged vessel with plain muscle developed in its wall is very often mistaken for a vein. In persistent lymphatic obstruction as with chronic venous obstruction, oedema makes its appearance from the passage of fluid into the tissue spaces. Distension of the smaller lymphatic vessels may be so marked as to be followed by rupture and this accounts for the chyluria and chylous ascites of filariasis, resulting from intra-abdominal blockage.
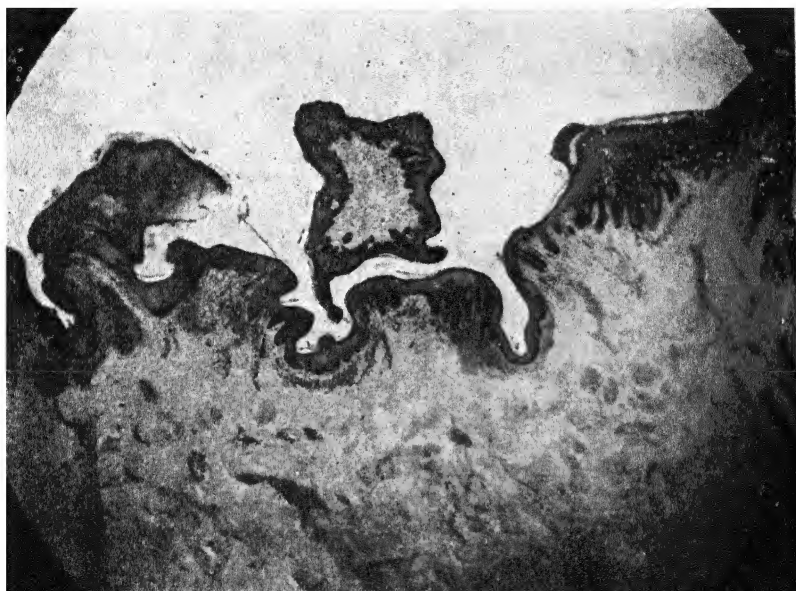
THE PATHOLOGY OF ELEPHANTIASIS.

Matas defines elephantiasis as a progressive chronic inflammatory fibromatosis or hypertrophy of connective tissue on the assumption that mere mechanical obstruction is not enough to produce this condition. This is, no doubt, consequent on the earliest descriptions of Sabouraud (1892)[75] on non-tropical elephantiasis, as due to the presence of bacteria in the tissues. Matas[90] (1913) and also Sustrunk[91] (1923) regarded bacterial inflammation as necessary for the development of elephantiasis, though not as its primary cause. Even in tropical elephantiasis, they regard filaria, as not the essential cause in the production of lymph stasis. However, the existence of a type, with solid thickening of the skin, with the development of nodules and papillae without febrile attacks, is mentioned in the early Hindu writings of Sushruta (about 6th century B.C.). It is now more or less accepted that elephantoid oedema may occur without inflammation; that persistent and long continued lymphatic obstruction is followed by elephantiasis. The experimental production of elephantiasis in dogs by Homans, Drinker and Field[92] (1934) by injection of sclerosing solutions into the main lymphatic trunks has been followed, in the long run, by typical elephantiasis, without any febrile attacks. It is now recognised that the mechanical factor is the essential feature. A blockage of the main lymphatic trunks, especially as they converge at the root of the

limb, where all the lymphatic trunks pass through the important filter beds, the superficial and deep lymph nodes—this is the lesion that results in elephantiasis. A study of the lymphatic circulation of the lower limb will demonstrate that all the superficial and deep lymphatic trunks in front converge just below the inguinal canal, forming as it were, an isthmus which connects the femoral with the pelvic lymphatics. In elephantiasis, this isthmus is blocked up and the lymph settles in the lower limb. This blockage might be due to lesions caused by parasites as in filariasis; to tumours blocking the deep lymphatics as in carcinomatosis; from septic lymphangitis followed by lymphatic obstructions in various forms of surgical sepsis, in skin diseases, and in phlegmasia alba dolens, from operative removal of the main lymphatic glands; from injuries involving the circumference of the limb (Matas), followed by fibrosis; and from post inflammatory fibrosis from syphilitic or yaw ulceration (Manson Bahr). Hereditary and familial oedema or Milroy's disease is believed to be due to lymphatic stenosis, probably congenital.

Morbid anatomy of elephantiasis.—

Elephantiasis generally affects the limbs, most often the lower limbs, but occasionally there are cases, where the upper limbs are involved. The involvement of the genitalia, especially the scrotum, is commonly met with and less frequently the pectoral region and breasts are involved. The skin and subcutaneous tissues are chiefly involved but the change spreads in the later stages in

Photomicrograph XI showing hypertrophy of the skin and the formation of papillomatous masses in elephantiasis. (x 25)

the fascial planes in between muscle bundles right down to the bone. As a consequence, a pressure atrophy of the bone may also occur. The skin may be smooth in one type, but commonly there is a hypertrophied thickening with exaggeration of the normal folds and furrows. In advanced types, nodular elevations of variable size make their appearance, while in other cases, the skin becomes cornified and thrown into folds, so that multiple papillomatous masses are formed. This has been called the stage of pachydermia. In some cases, the external cuticle is desquamated and an eczemtous weeping state may occur in a moist and sudden area. In others, the surface of the skin may be inflamed and mild erysipelas may be met with. Occasionally, the nodular masses may fall off and chronic ulcers may result. In some cases, diffuse cellulitis may involve the sodden tissues and occasionally localised abscesses or deep seated suppuration may occur.

Persistent lymph stasis in the lymphatic system is followed by oedema, which gradually becomes firm and solid owing to the development of collagen. The appearance on section is that of a moist loose "blubber" like tissue that is characteristic of early elephantiasis. Later the tissue becomes firmer, and more dense and difficult to cut.
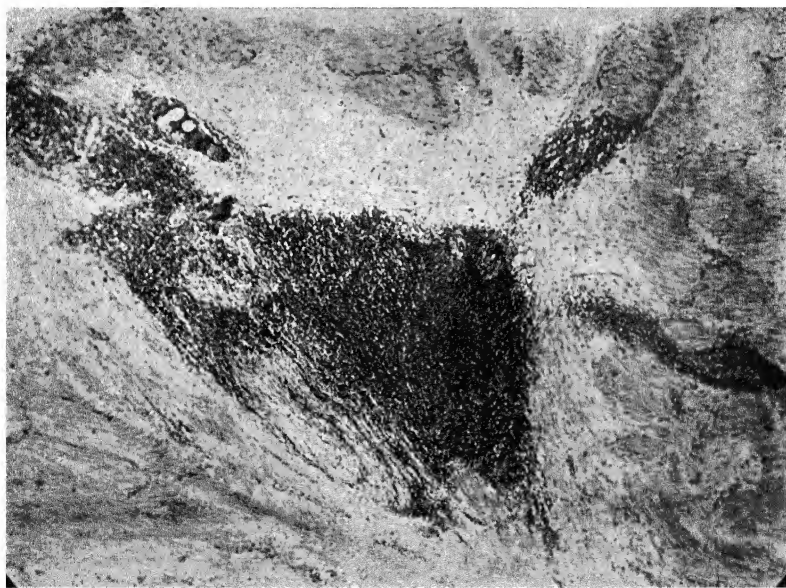
The histological changes.—

Our own histological studies on elephantoid tissue tend to show that there are two distinct types of the condition; one, where the lymphatics involved show

well marked signs of chronic inflammation and
the other, where the inflammatory signs are
absent. The changes in the skin consist in many cases
of a hypertrophy of the papillary folds with some
increased keratinization of the squamous cells. A true
hypertrophy and multiplication of the layers of
epithelium is not marked in our experience. A
remarkable feature, that is met with, is the dilatation
of the superficial lymph capillaries just under the skin.
These vessels which are hardly visible in the normal
skin become very prominent and appear as irregular
slits lined by flat endothelium. This extensive develop-
ment and dilatation of the superficial capillary
bed has also been noticed in experimental elephantiasis
in dogs, following the injection of sclerosing solutions
into the lymphatics. (Homans, Drinker and Field). It
is an expression of a collateral drainage, a flow back
from the normal lymph conduits, which are obstructed
through the capillary bed under the skin. This esta-
blishment of a collateral circulation is much more
marked in the non-inflammatory type of the disease.
In the inflammatory type, though there is a dilatation of
the superficial capillary bed, each vessel is surrounded
by a cluster of lymphoid cells, indicating that a chronic
lymphangitis has spread to the small vessels as shown
in photomicrograph 12. While this lymphatic dilata-
tion is most marked in the capillaries under the skin, a
careful study of the deeper structures will show that it
is also present in the fine capillaries in between the
muscle bundles and fasciae, the deep capillary bed.
The lymphoid infiltrations are so marked in some cases,

Photomicrograph XII showing **keratinization** of the skin, hypertrophy of the papillae, and the dilatation of the lymph capillaries under the skin. The capillary vessels are surrounded by clusters of lymphoid and plasma cells, indicating a chronic lymphangitis.   (x 50)

Photomicrograph, XIII showing lymphoid cells forming dense clusters in between muscle bundles in elephantiasic tissues.   (x 50)

that groups of cells may appear as lymph follicles in the deep tissues. While lymphoid cells predominate, plasma cells are also met with. The picture is that of a chronic inflammation affecting the lymphoid vessels both superficial and deep. While these changes vary in the inflammatory and non-inflammatory types of the disease, a more striking feature is the progressive fibrosis of the subcutaneous tissues. Here cells are scanty, but collagen fibres are developed in abundance and form irregular strands separating structures and passing down between muscle fibres. We have also observed the formation of elastic fibres, but these are more irregular and mostly on the surface. Between the masses of fibrous tissue, the normal slits or tissue spaces are much more developed than normal. These have no endothelial lining as the lymph capillaries but are merely crevices of tissue. These spaces are so numerous that the collagen bundles are split up into thin strands separated by fluid. The oedema of early elephantiasis and the formation of blubbery tissue appear to be due to the passage of lymph from the lymph capillaries into these spaces, which are 'the ponds, and lakes', distinct from the lymph capillaries.

Aetiology and pathogenesis.—

What is the exact machanism of causation and what are the causative factors in tropical elephantiasis? Here again, there are conflicting schools of thought. On the one hand, we have the view from the time of Sonsino[93] (1882) that the parasites are directly responsible for the fibrous overgrowth which is an expression of irritation of the tissues. Bahr[94] (1913) has pointed

out that the continual irritation by calcified and dead filariae in lymphoid tissues is followed by extensive fibrosis. O'Connor (1932), in his recent work, has demonstrated that hyperfilariation is common, and that in many cases a number of worms are present. The radiographic studies of O'Connor, Golden and Auchincloss[95] (1930) have shown that the calcified tombstones of the dead worms are scattered about the elephantoid tissue. That their death is followed by encapsulating reactive formations of granulomatous nodules in the lymphatic vessels and in the neighbourhood of lymphatic glands and also followed often by obstructive lesions and consequent lymph stasis, we have already demonstrated. Elephantiasis is thus looked upon as the result of persistent mechanical obstruction. The lymph is dammed back to the tissue spaces, becomes more concentrated and altered in composition and leads to the development of collagen owing to the increasing pressure in the affected tissues.

Another view takes into account the importance of bacterial infections, in the development of the fibrosis, on analogy with the non-tropical type. According to this view, the sequence of events is briefly that filariae cause lymph stasis owing to mechanical changes, that the stagnant lymph is a favourable culture medium for bacterial growth, that secondary infections occur in consequence and that this bacterial lymphangitis causes a progressive thickening of the skin, resulting in elephantiasis. Acton and Rao[96] (1933) claim that their bacteriological findings afford proof of the importance

of these secondary infections in the production of elephantiasis.

Do the microfilariae play any part in the production of fibrous overgrowth? It is well known that microfilariae are not often found in the blood, in cases of elephantiasis. It is possible that live worms lying in obstructed lymphatics may discharge their brood into the lymph spaces. Such live worms have frequently been found lying in the distal lymphatics in elephantiasis. It is also now known that the microfilariae give rise to reactive changes, when they are destroyed in the tissues and lymphatic glands. I have often asked myself, if the microfilariae play any part in the production of the fibrous overgrowth in elephantiasis. In obstructed lymphatics, do they lose their sheath and bore their way into the tissue spaces or are they merely destroyed round about the parent worms? In Onchocerca infections, we have an instance of filarial larvae causing irritative overgrowth in the subcutaneous tissues? Can a similar state of things happen in elephantiasis?

In many cases, as already mentioned, histological studies tend to show that elephantiasis can be produced by mere mechanical obstruction without inflammation. Are the attacks of elephantoid fever that complicate some cases due to bacterial infections or are they merely allergic reactions due to the death of the worm or to toxic products discharged from the worm? It is easy to understand how secondary infections can complicate elephantiasis. The collateral circulation is through the lymph capillaries just below the skin: infections can

easily occur from minute abrasions in the skin. There are definite clinical types, as mentioned from the time of Sushruta, where the skin gets fissured and inflamed and a thin serous discharge escapes from the surface. A complicating and mild erysipelas can and does occur in some cases. Even in experimental elephantiasis in the dog, Homans, Drinker and Field have recorded attacks due to complicating bacterial infections after the elephantoid condition has persisted. Such infections, however, seem to me to be late events or complications that play no direct part in the pathology of filarial elephantiasis.

METHODS OF DIAGNOSIS.

The examination of the blood from a finger prick under a cover glass ringed round with vaseline is the time honoured method. The picture of the embryos wriggling about under the cover slip is convincing for even the uninitiated. This method, however, is at the best a messy job and we have abandoned it in favour of thick drops or thick films. The films are dried and can be conveniently examined after dehaemoglobinisation in water or saline and staining with Leishman's stain. It is always an advantage to take a measured quantity of the blood and follow Low's[97] technique of drawing up in a leucocyte pipette 10 cmm. of blood and prepare thick films. A definite microfilarial count can then be recorded. For a study of structure and differentiation of species, Feng[98] recommends staining with methyl blue pyronin after dehaemoglobinisation in saline. The slides are over stained by prolonged staining and then
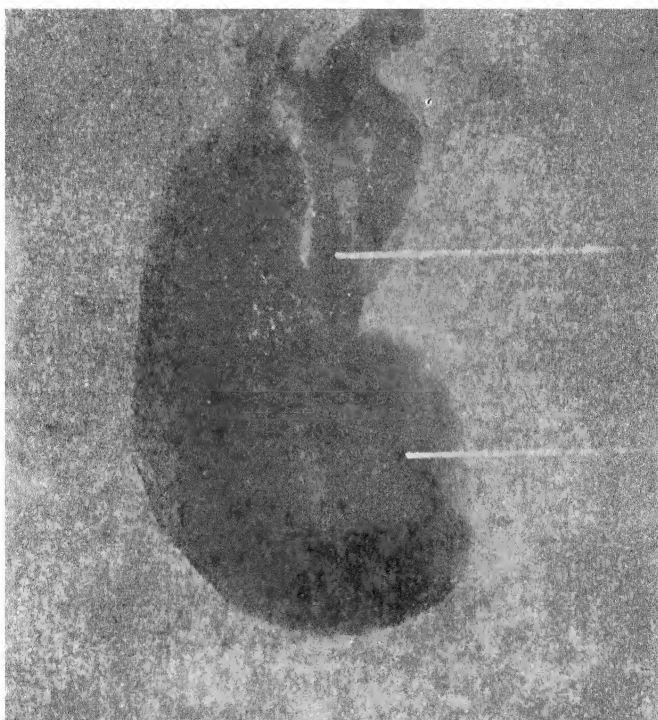
differentiated in graded alchohols and finally mounted in balsam. In cases where scanty numbers are found in the peripheral blood, Staubili's method[99] of taking 5 c.c of blood from the vein may be carried out. The blood is immediately laked by adding to it fifteen volumes of 3% acetic acid, shaken up to prevent clotting, centrifugalized and the sediment examined.

Diagnosis by serological and intradermal reactions has been introduced by Fairley by using an extract of the dog filaria, *Dirofilaria immitis*, as the antigen. The complement fixation reaction is carried out on the same lines as the Wassermann test with an alcoholic extract as the antigen. This reaction has been carried out on a large scale at the Calcutta School of Tropical Medicine and has given variable results. On the other hand, the intradermal reaction first introduced by Talliaferro and Hoffman[100] (1930), by using 0·5% of the saline extract of the dried worms and injecting 0·25 c.c. intradermally has given very satisfactory results. Subsequently, Fairley[101] used 0·25 c.c. of the extract. A typical immediate reaction is described by Fairley as a diffuse erythema following a wheal with branching extensions, altogether measuring about 2·3 cm. in diameter or larger. Delayed reactions are also recognized where extensive swelling and redness of the arms occur in twenty-four hours. Extended trials of the intradermal tests have shown that this is a valuable diagnostic method in the clinical study of filariasis. Unfortunately, the difficulty in obtaining the antigen in India has prevented a more extensive application of this test. Since this is regarded

as a group reaction given by other filaridae it is possible that we have, in *Dirofilaria repens,* which is found in some parts of India, a suitable material for the preparation of antigen.
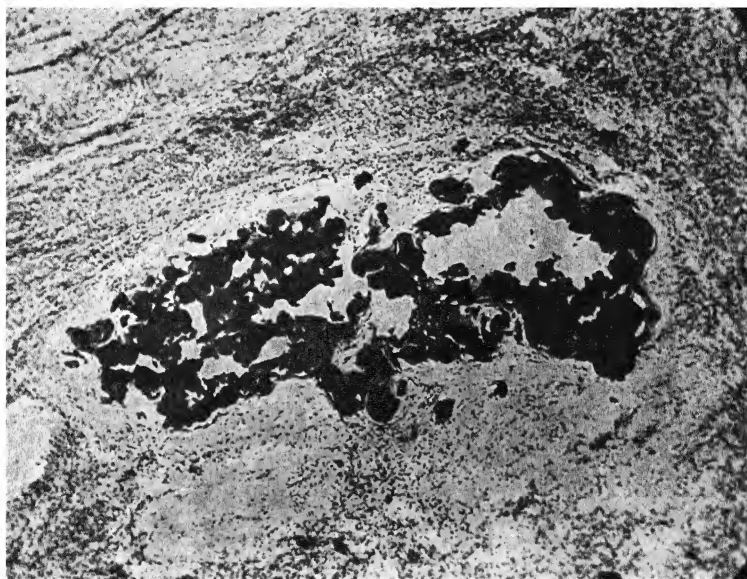
Radioscopic diagnosis.—

The radiological work of O'Connor, Golden and Auchincloss has brought to us a modern method of diagnosis of very great importance. By using a plain film, a fine focus tube, and technique calculated to give soft tissue detail, minute shadows of clacium density have been made out on the film in cases of filariasis. These are very minute, about ·1 to ·3 mm. in size and so small as can only be made out with a lens. Microscopic streaky calcification of the worm as made out histologically, *may not* sometimes be detected on the film owing to the minute size of the calcium deposit. Calcified arteries can easily be distinguished since these shadows have obviously different shape and are often considerably larger, thicker and more oval. A comparison of the radiographic shadows of calcified filariae in pathological tissues removed by operation with those obtained from clinical cases would demonstrate their identity. These shadows, which vary in size from about 1 mm. in width to about 3-4 mm. in length either appearing as continuous lines or as broken spots like chains of cocci have been definitely proved to be calcifying adult worms by surgical removal and histological sections by O'Connor and his colleagues. In clinical cases of elephantiasis, they can be demonstrated in the elephantoid leg, especially in Hunter's canal and in the
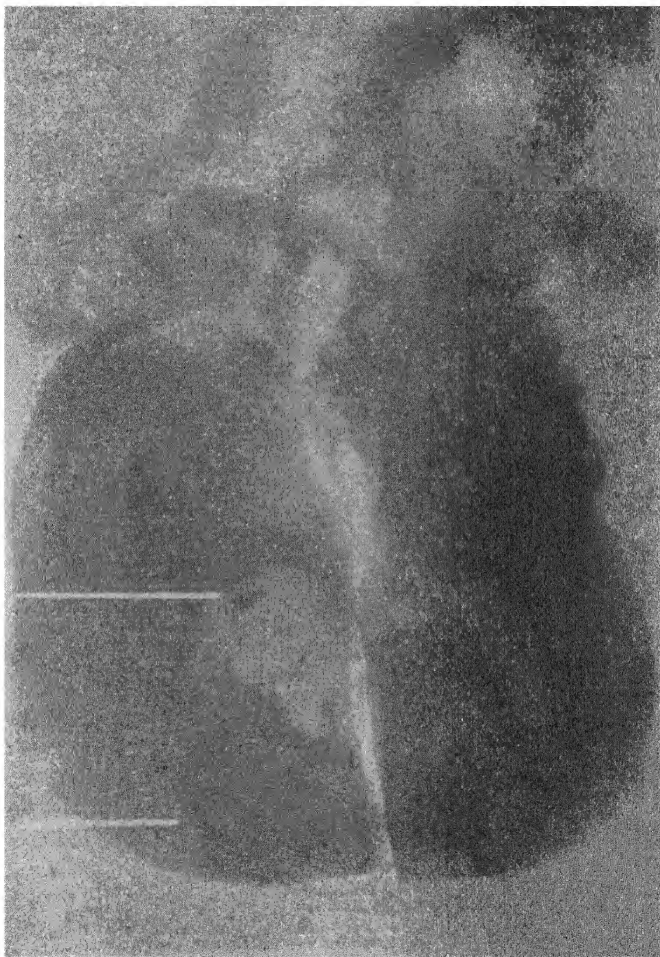
Radiogram of the testis. (Epididymo-orchitis—Case I) showing two small opacities, one on the tunical albuginea and the other, in the epididymis. Four recently dead worms were found in the testis. The small opacity in the tunica albuginea is a calcified worm in a lymphatic vessel. (Photomicrograph XIV).
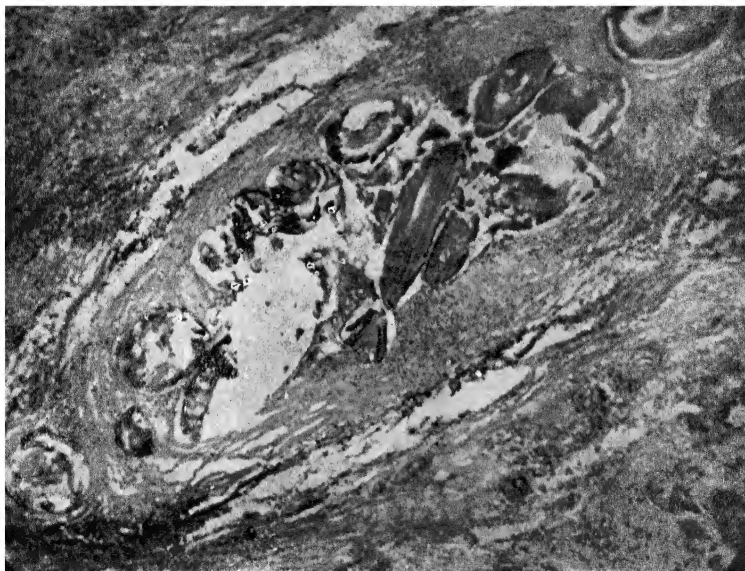
Photomicrograph XIV showing the remnants of a completely calcified worm in a lymphatic vessel. This corresponds to the opacity shown in the filarial testis in Case I. (x 50).

Radiogram of the testis—Case II, showing two large opacities due to irregular calcification in the wall of the hydrocele sac and a small faint opacity due to commencing calcification round the worm. The photomicrograph shows the worm.

Photomicrograph XV showing early calcification of a filarial worm in the lymphatics of the testis. This corresponds to the opacity marked in the photo of chronic epididymo-orchitis—Case II. (x 50)

streaky mottling of the subcutaneous fat under the skin. In the genitalia, the spermatic cord is the favourite site as also the epididymis and the testis. They have also been found in the scrotum and the lymph nodes. Very often they are quite superficial under the skin in the lumps of fat in the subcutaneous tissues. The radiographic demonstration of these shadows in clinical cases is not only of value in the diagnosis of filarial infections such as in obscure cases of orchitis, funiculitis or hydrocele, but they give us exact data regarding the situation of the worms. It has also been found that, in many cases, the live worms live in close proximity to those showing calcification and this feature is of immense importance, as we shall see, in the therapeutic attack of the worms.

Radiographic studies carried out at the Government Rayapuram Hospital, Madras, in collaboration with Dr. Sundaresh, the Radiologist, have confirmed the value of these methods in diagnosis not only in clinical cases, but also in pathological tissues. We have been able to confirm histologically the significance of these small shadows found on films, described by O'Connor, Golden and Auchincloss. The pathological specimens examined consisted of specimens of filarial testis, and elephantiasic tissue. As shown in the X Ray films, small oval and irregular shadows are noticeable in the radiograms in all these cases. We have also sections of the tissues showing the calcified filaria. Pieces of tissues taken from all the sections showed the worms, as can be seen from the accompanying photomicrographs. There are also

radiograms from cases of elephantiasis, which show similar opacities of calcium density, but these have not yet been confirmed histologically. In another case of suspected lymphangitis, in the arm of a young medical student, radiograms taken after an attack had subsided showed fibrous oval density in the region of the epitrochlear gland and two small foci of calcium density just under the skin of the fore arm below, as shown in the radiograph.
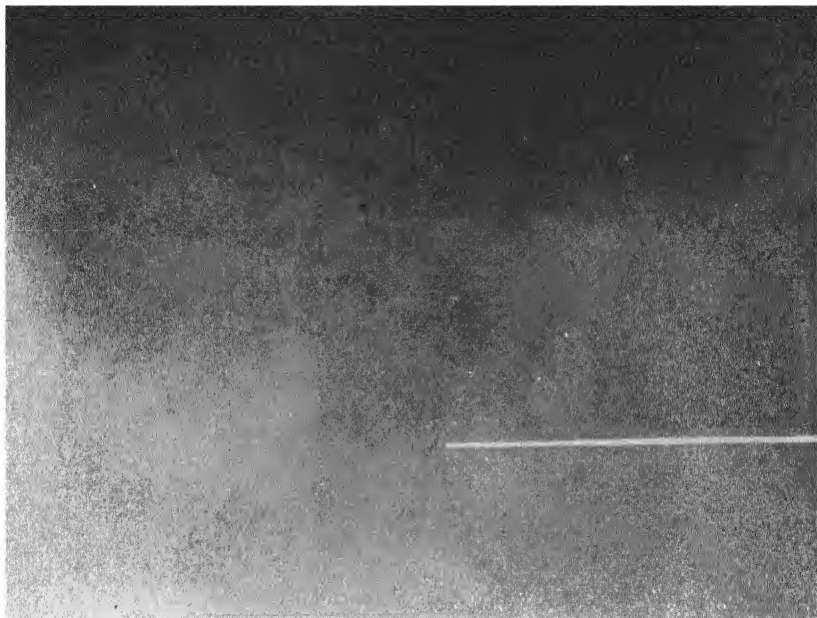
The phenomenon described by Pandit, Pandit and Iyer[102] (1929) of adhesion of the leucocytes to the microfilariae when they are brought into contact with serum from a case of elephantiasis has also been made use of in diagnosis. It appears that some antibody is present in these cases of elephantiasis when microfilariae are absent from the blood. This antibody brings about adhesion of the leucocytes to the microfilariae, and this is in turn followed by disintegration of the parasite. The effect appears to be specific for *M. bancrofti,* since the microfilaria of the crow and of the lizard are unaffected.

The significance of this work, if confirmed in a large number of cases, is that we would have a delicate serological test for the differentiation between filarial and other types of elephantiasis. When the radio-scopic picture is inconclusive and with an indefinite history and with the usual absence of microfilariae in the blood, clinical differentiation may become a difficult problem.

Radiogram of elephantiasic tissue from the scrotum, showing small opacities of calcium density in the centre. No. 1 has been found to be a calcified worm in a lymphatic vessel.

Radiogram of a case of filarial epididymo-orchitis with hydrocele, showing a linear shadow, about 3 mm. in length, lying in the wall of the sac.

Radiogram of a case of filarial lymphangitis of the arm, showing two small opacities, cocoid in shape, just under the skin and a large opacity of fibrous density in an enlarged epitrochleal gland.

THE PROBLEMS OF TREATMENT.

In the course of the discussions regarding the pathology of the disease, I have tried to divide the subject into filariasis proper and its septic complications. This is on the view of the verminous responsibility for the essential lesions. Secondary septic infections no doubt complicate clinical cases and suppurative lesions and erysipelatoid inflammations result. The distinction between the disease and its complications, is of very great importance when we take up the problems of treatment.

Treatment with antimony compounds is the time honoured method in India of therapeutic attack of the worms. Tartar emetic has been gradually replaced by the newer antimony compounds such as urea-stibamine and stibosan. The results have been variable. Organic arsenicals have also their advocates and cases where the attacks have subsided have been recorded (Dalal[103] 1927). Gold therapy has also been tried, but all these methods have been disappointing as vermicides. The difficulty has been to obtain a drug that would be in effective concentration in the blood and lymph to destroy the parasites without damaging healthy tissues.

With the discovery of complicating microbic infections in filariasis, medical treatment by injections of anti-streptococcal vaccines came into prominence and Rose (1919) claimed good results in cases of lymphangitis in Porto Rico by two successive doses one of 100 millions followed by another of 200 millions. Similar results have been recorded by Anderson; and thus vaccine treatment came into vogue and has been

very popular with the profession in India. Gradually however specific vaccine treatment by increasing doses became replaced by weekly injections of large doses of any vaccine, the idea being that any benefits are really due to a non-specific effect. For this purpose T.A.B vaccine, various antisera, and even oil of chinapodium, all these have been used.

Of newer methods of treatment one that is of great interest is that described by O'Connor[104] (1929) of injecting sulpharsephenamine. The importance of a local spot of itching and tenderness in the inflamed area, the signal lesion, has been interpreted by O'Connor as being due to the location of the worms. 0·2 g. of sulpharsephenamine were dissolved in 2 cc. of sterile 1% novocaine solution and injected into the tender spot. Cases with recurrent monthly attacks were selected. Of twenty cases so treated 18 had no further attack. Two others had attacks but these were in other situations. In this method, we have a mode of directly dealing with the parasites that is not only rational but simple. The difficulty would be in the location of the worms if the tender spots described by O'Connor are not met with. Radiography might however give a clue which may be of value. Organic antimony preparations may also be tried as a mode of local treatment and in any case a trial of the aniline dyes such as trypan blue or methylene blue, it seems to me, may prove to be of value.

Surgical measures.—

A local surgical removal of the worm has also been attempted on these lines and has given encouraging

results.   Tender spots have been excised, and patho-
logically verified.   In cases where there is difficulty, the
worms may be located by stereoscopic radiology, taking
the calcified worm as the index of location.   These
promising methods of surgical treatment are certainly
worthy of more extended trials in India where we have
filariasis in all its abounding clinical varieties.

Of operative procedures in restoring the lymph
circulation in elephantiasis or in removing elephantiasic
fibrosed tissues it is not possible to discuss fully in the
course of these lectures.   Sir Frank Connor[105] favours
the Kondoleon[106] procedure (1912) of a removal of a
portion of the fascia lata in order to bring about an
anastomosis between the superficial and the deep
lymphatics.   Handley's operation of lymphangioplasty
by the insertion of deep silk threads to induce drainage
does not take into account the essential cause of the
disease. It has also not been attended with any striking
results.   Auchincloss[107] (1930) advocates a method of
removal of the sclerosed tissues leaving the skin flaps
entire so as to ensure continuity of drainage.   It must
be remembered in this connection that the old method
of free removal of elephantiasic tissues almost right
down to the muscle, followed by skin grafting, has the
advantage that it does away with all diseased tissues as
well as *the parasites that are present*.   The importance
of preserving the skin intact is, emphasized by the
studies of Homans, Drinker and Field, as they have
shown by injections of trypan blue that the collateral
circulation is carried out by the superficial lymph
capalliaries just under the skin.   Theoretically at

least, in tropical elephantiasis, a combination of the old method of free removal combined with a technique to retain the skin entire may be of value.

NEED FOR FURTHER WORK.

Before concluding I must reiterate that all these filarial problems are not solved. Histological, cultural, and experimental studies are required and on a more extensive scale than have been carried out.

Nearly eight years ago, Sir Frank Connor pleaded for a more extensive and thorough investigation of the filariasis problem and even to-day I have only to repeat this plea. There are many features of the disease that baffle explanation and mere explanation is not enough. We want more accurate and more complete data. Inference will follow of itself.

As an instance, I have already pointed out that the basic theory of mosquito transmission becomes weak when we take up the question of variation in types, unless we believe in an instinctive migration of the worms, that varies with the endemic focus. A definite type, elephantiasis of the external genitalia, especially of the scrotum in the male, is too frequent an occurrence to be explained by a haphazard wandering of the worms from one set of lymphatics to those drainage a different area. Is there a mode of entrance of the larvae from the external genitalia? I would plead for an investigation of the old and discarded theory of water transmission. Popular beliefs have sometimes a grain of truth. The example of the mosquito transmission of malaria

is a striking instance. If infective filarial larvae can possibly get in from infected water, it is easy to understand how prevalent customs in India would contribute to a genital lesion since water in ponds and tanks is frequently used for cleaning and toilet purposes. Occupational filariasis among coir culti-vators in Cochin and Travancore would mean only a greater incidence among those who come into contact with infected water. If the infective larvae are present in water, they can easily be recovered by adding formalin and centrifugalisation. The problem can also be tackled from the laboratory with filariated mosqui-toes brought into contact with water. It seems to me that this question can then be settled once for all.

Studies on the infective larvae from the mosquito, on their longevity and on their reaction to different environment, studies on the course of the larvae, and the tissue reactions in experimental infections, are all urgently needed to settle the problem of transmission.

With regard to filarial surveys, it may be said that a house to house survey, as carried out in Saidapet, based on the census population of the affected part is likely to give a more reliable index of the rate of infection rather than one based on an examination of a group of people round about.

Of further histological studies on the glands and infected tissues there is no need for special emphasis. With regard to problems of microfilarial periodicity, we have in India an abundance of clinical material to test Lane's theory of cycle parturition. Removal of

the glands and other filariated tissues could be accurately timed by the surgeon. Parturition of the periodic worms in Madras, if it is simultaneous, would probably occur at about 11 A.M. in order that the embryos may have time to travel up the tortuous 'lymph escalator' and concentrate in the blood at about 11 P.M. every night.

It is only by accurate and co-ordinate studies, clinical, laboratory and in the field, that further knowledge can be gained, and of all these, I would lay more stress on clinical studies. Accurate and definite information obtained from one case, if co-ordinated by an examination of tissues, is of much more value than theories based on insufficient evidence, in a disease where theories already abound.

To those who are just about to enter the profession after qualifying, in whom the spirit of research is beginning to glimmer, there is, in filariasis, work for a lifetime. They can do nothing better in life than in a work of this kind. To those, who as practitioners of the art of medicine are sometimes inclined to work in a groove to follow emperic and advertized lines of treatment I would like to preach the doctrine of doubt, or even of disbelief, when it comes to filariasis; and to those research workers, who claim that all these filarial problems are solved, I would commend the words of Sir Isac Newton,

"I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing

on the seashore, and diverting myself in now and then finding a smoother pebble, or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."

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ERRATA.

Page.	Line.	for	read
10	13	more	mere
16	17	albugineca	albuginea
29	15	vaiegatus	variegatus
56	6	chinapodium	chenopodium
57	last line	capalliaries	capillaries
58	25	drainage	draining
60	23	emperic	empiric